action, at page 13, lines 4-7, the Examiner stated

> Claim 63 is a method which depends from claim 46, which is canceled. Because there are no other method claims in the instant application, it is not clear what this claim encompasses. Therefore, the claim is indefinite and cannot be examined with regard to enablement, written description, or art issues.

In our July 28 paper, we commented (page 11, §§1.2-1.3):

> 1.2. The Examiner failed to examine 63 because it is dependent on a cancelled claim. While that is ground for rejection (MPEP §608,01(n)(V)), the claim should still have been examined on its merits. See 37 CFR §1.104(a)(1) and (b) and MPEP §707.07(g).
>
> 1.3. For the reasons set forth above, i.e., the failure to grant an interview and the failure to examine 63 on its merits, the next action, if a rejection, should not be made final.

Judging just from page 13 of the January 31 action, it would have been more accurate to say that the examination of claim 63 was admitted to be incomplete and hence, if claim 63 were subsequently examined and rejected "with regard to enablement, description, or art issues", that new action could not be made final.

However, claim 63 was not listed in the statement of claims rejected under 112 ¶2 in the beginning of §9 of the office action, leading to doubt as to whether it was rejected for indefiniteness or merely not examined. The Examiner has conceded the inconsistency, hence the issuance of the supplemental action.

2. Like the original action, the supplemental action does not reject claim 63 on any ground other than indefiniteness, and that based solely on its prior dependency on a cancelled claim.

Claim 63 was introduced by the January 22, 1998 amendment, reading "The method of claim 46 in which the subject is human". The same amendment rewrote claim 46 in independent form; previously 46 was dependent on DNA claim 40.

Claim 46 was cancelled by the September 10, 1998 amendment. One solution to the dependency problem with claim 63 was therefore to make it dependent on DNA claim 40, which remains pending. DNA claim 40 in turn is dependent on DNA claim 10. Another possible solution was to rewrite it in independent form, in which case it need not retain the "Cunningham proviso" of claim 10.

The July 28 amendment in fact rewrote claim 63 in independent form. Hence, the alleged indefiniteness of claim 63 was already overcome at the time the supplemental action was mailed and there was no reason not to examine it with regard to enablement, written description, and art issues.[1]

Hence, if the next action rejects claim 63 on any ground other than indefiniteness, it cannot be made "final", as that would then a new ground of rejection not necessitated by Applicants' amendment, See MPEP §706.07(a). In this regard, note that for the reasons mentioned above, the Examiner could and should have examined claim 63 as to <u>all</u> issues prior to July 28, even though it was dependent on a cancelled base claim. Rejection on enablement or prior art grounds is not "necessitated" by the July 28 correction of dependency as such rejections may be applied to claims which are also considered indefinite. See MPEP §2143.03. This is consistent with the

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[1] Indeed, even if the indefiniteness rejection had not been overcome, the failure to examine it as to all issues was improper. See MPEP §2143.03, requiring consideration of indefinite (and "new matter") limitations when make a prior art rejection. The claim should then have been construed as if it included all limitations of the cancelled base claim.

general policy that actions be as complete as possible. MPEP §707.07 and 37 CFR §1.104.

Consequently, we do not agree with the Examiner's statement, on page 4 of the Action, that "it would appear that the next action could properly be made "final". It all depends on how claim 63 is treated.

Respectfully submitted,

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Enclosure
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10. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first vertebrate growth hormone residue where

(i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone,

wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

11. The DNA molecule of claim 10 wherein the differences as specified in (B)(II) are solely amino acid substitutions as set forth in (a) and (b).

12. The DNA molecule of claim 11 wherein, for all non-conservative substitutions, both of conditions (II)(b)(i) and (II(b)(ii) apply.

13. The DNA molecule of claim 11 wherein all substitutions are conservative substitutions as defined in II(a).

14. The DNA molecule of claim 11, said amino acid sequence having at least about a 66% identity with the sequence of said first reference vertebrate growth hormone.

15. The DNA molecule of claim 10, said amino acid sequence having at least about a 80% identity with the sequence of said first reference vertebrate growth hormone.

16. The DNA molecule of claim 11, wherein substitutions of residues in the third alpha helix are limited to residues corresponding to bGH residues Gly119, Ala122, Leu123, Ile120, Leu116, Asp115 and Glu118.

17. The DNA molecule of claim 11, wherein the third alpha helix is at least 50% identical to the third alpha helix of said first reference vertebrate growth hormone.

18. The DNA molecule of claim 11, wherein the third alpha helix is at least 80% identical to the third alpha helix of said first reference vertebrate growth hormone.

19. The DNA molecule of claim 11, wherein the non-conservative substitutions, if any, are all of residues other than those belonging to conserved domains GD1 (hGH 9-31), GD2 (hGH 53-68), GD3 (hGH 75-93), GD4 (hGH 114-130) and GD5 (hGH 162-189).

20. The DNA molecule of claim 11, wherein the non-conservative substitutions, if any, are all of surface residues.

21. The DNA molecule of claim 11, wherein each non-conservative substitution, if any, is with a replacement amino acid found at the corresponding position in a vertebrate growth hormone, prolactin, placental lactogen, or other hormone homologous to human growth hormone, or with an amino acid which is a member of the same exchange group as an amino acid found at the corresponding position in a hormone homologous to human growth hormone.

22. The DNA molecule of claim 11, wherein each non-conservative substitution, if any, is with a replacement amino acid found at the corresponding position in a second vertebrate growth hormone, or with an amino acid which is a member of the same exchange group as an amino acid found at that the corresponding position in a second vertebrate growth

hormone.

23. The DNA molecule of claim 11, wherein each non-conservative substitution, if any, is with a replacement amino acid found at the corresponding position in a vertebrate growth hormone, prolactin, placental lactogen, or other hormone homologous to human growth hormone.

24. The DNA molecule of claim 11, wherein each non-conservative substitution, if any, is with a replacement amino acid found at the corresponding position in a second vertebrate growth hormone.

25. The DNA molecule of claim 11 in which the first reference vertebrate growth hormone is a mammalian growth hormone.

26. The DNA molecule of claim 11 in which the first vertebrate growth hormone is a human or bovine growth hormone.

27. The DNA molecule of claim 11 in which the substitution (I) is with an amino acid at least as large as proline.

28. The DNA molecule of claim 11 in which the substitution (I) is with an amino acid selected from the group consisting of Arg, Trp, Pro, Lys and Leu.

29. A purified or non-naturally occurring DNA molecule which comprise a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence comprising residues corresponding to residues 96-133 of bovine growth hormone which sequence is at least 50% identical to the amino acid sequence of a first vertebrate growth hormone, and wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is an amino acid other than glycine or alanine, said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R,

G120L, Q122E, T123G, G126L, R127I and E129S.

30. The DNA molecule of claim 29 wherein said amino acid sequence is at least 66% identical to the amino acid sequence of the first vertebrate growth hormone.

31. The DNA molecule of claim 29 wherein said amino acid sequence is at least 80% identical to the amino acid sequence of the first vertebrate growth hormone.

32. The DNA molecule of claim 29 wherein said amino acid sequence is at least about 90% identical to the amino acid sequence of the first vertebrate growth hormone.

33. The DNA molecule of claim 29 wherein said first vertebrate growth hormone is human or bovine growth hormone.

34. The DNA molecule of claim 11 which has an ED50 which is less than about 10 times the ED50 of the first vertebrate growth hormone in an assay of the ability of the polypeptide to displace radiolabeled first vertebrate growth hormone from a liver membrane vertebrate growth hormone receptor.

35. A purified or non-naturally occurring DNA molecule which comprises a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and either

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first vertebrate growth hormone residue,

(b) a substitution of a non-conservative

replacement amino acid for the corresponding first vertebrate growth hormone residue where

(i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said first vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(b) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second vertebrate growth hormone,

said polypeptide having a statistically significant inhibitory effect on the growth of transgenic mice engineered to produce said polypeptide, as compared to the growth of equivalent nontransgenic mice,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

36. The DNA molecule of claim 35, wherein the ratio of the growth rate of two month old transgenic mice expressing

the polypeptide, to that of their nontransgenic litter mates, is not more than 0.96:1.

37. The DNA molecule of claim 11 wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is substituted with an amino acid other than proline.

38. The DNA molecule of claim 11 wherein the mutations include at least one substitution according to (II) above which is of a residue which is part of an alpha helix of said first vertebrate growth hormone and which substitute amino acid has a greater alpha helical propensity than did the corresponding residue of said first vertebrate growth hormone.

39. The DNA molecule of claim 38 wherein said first vertebrate growth hormone is bovine growth hormone and said helix corresponds to the third alpha helix of bovine said first vertebrate growth hormone.

40. The DNA molecule of claim 10, further comprising a promoter operably linked to said coding sequence whereby said polypeptide may be expressed in a host cell compatible with said promoter.

41. The DNA molecule of claim 40, wherein the promoter is a regulatable promoter.

42. The DNA molecule of claim 40 which is a retroviral vector.

43. The DNA molecule of claim 40 which is a linearized DNA.

44. A cell transformed by the DNA molecule of claim 40, and which expresses said polypeptide.

45. A nonhuman transgenic animal, at least some of whose somatic and germ cells contain the DNA molecule of claim 40, and which expresses said polypeptide under promoter-activating conditions.

62. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

(e) an insertion of a residue at an insertion point outside the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such insertion point furthermore not being between conserved residues in the vertebrate GH family, and

(e) an insertion of a residue absent in said first reference vertebrate growth hormone but present in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

63. A method of reducing growth hormone activity in a mammalian subject which comprises administering to the subject a DNA molecule comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide, under conditions conducive to the integration of

said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

where said polypeptide comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone, wherein said corresponding residue,

which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said first vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second vertebrate growth hormone

whereby the growth hormone activity in said subject is reduced,

in which the subject is human.

65. The DNA molecule of claim 29 wherein the comprised amino acid sequence differs from said reference vertebrate growth hormone amino acid sequence solely by one or more amino acid substitutions.

66. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between

said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH

family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said first and second reference vertebrate growth hormones are both mammalian growth hormones.

67. The DNA molecule of claim 66 wherein the differences as specified in (B)(II) are solely amino acid substitutions as set forth in (a) and (b).

68. The DNA molecule of claim 66 wherein for all non-conservative substitutions, both of conditions (II)(b)(i) and (II)(b(ii) apply.

69. The DNA molecule of claim 66 wherein all substitutions are conservative substitutions as defined in II(a).

70. The DNA molecule of claim 66 wherein said amino acid sequence having at least about a 66% identity with the sequence of said first reference mammalian growth hormone.

71. The DNA molecule of claim 66 wherein said amino acid sequence having at least about a 80% identity with the sequence of said first reference mammalian growth hormone.

72. The DNA molecule of claim 66 wherein said amino acid sequence is at least about 90% identical to the amino acid sequence of said first reference mammalian growth hormone.

73. The DNA molecule of claim 66 where said first reference vertebrate growth hormone is human or bovine growth hormone.

74. The DNA molecule of claim 29 wherein the amino acid sequence of the antagonist comprises alpha helices corresponding to the alpha helices at about residues 4-33, 66-80, 108-127 and 150-179 of bovine growth hormone.

75. The DNA molecule of claim 11 wherein the amino acid

of (I) is arginine.

76. The DNA molecule of claim 11 wherein the amino acid of (I) is tryptophan.

77. The DNA molecule of claim 11 wherein the amino acid of (I) is proline.

78. The DNA molecule of claim 11 wherein the amino acid of (I) is lysine.

79. The DNA molecule of claim 11 wherein the amino acid of (I) is leucine.

80. The DNA molecule of claim 11 wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is substituted with an amino acid at least as large as leucine.

81. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

82. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 50% identical to the third alpha helix of bovine or human growth hormone.

83. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 80% identical to the third alpha helix of bovine or human growth

hormone.

84. The DNA molecule of claim 81 where said amino acid sequence is at least 50% identical with the amino acid sequence of bovine or human growth hormone.

85. The DNA molecule of claim 81 where said amino acid sequence is at least 80% identical with the amino acid sequence of bovine or human growth hormone.

86. The DNA molecule of claim 81 where the amino acid sequence of said mutant of said vertebrate growth hormone further comprises at least one substitution of another amino acid in said vertebrate growth hormone, where said another amino acid corresponds to an amino acid of bovine or human growth hormone which is not conserved among the vertebrate growth hormones.

87. The DNA molecule of claim 86 where said substitution of another amino acid is with an amino acid found at that site in a different vertebrate growth hormone.

88. A method of reducing growth hormone activity in a mammalian subject which comprises administering to the subject a DNA molecule comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide, under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,
where said polypeptide is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,

said polypeptide having mammalian growth hormone receptor

antagonist activity,

whereby the growth hormone activity in said subject is reduced.

89. The method of claim 81 wherein the mammal suffers from an excessive growth rate.

90. The method of claim 89 in which the mammal suffers from gigantism.

91. The method of claim 89 in which the mammal suffers from acromegaly.

92. The method of claim 88 wherein the mammal suffers from diabetes.

93. The method of claim 88 in which the mammal suffers from diabetic retinopathy.

94. The method of claim 88 in which the mammal suffers from glomerulosclerosis.

95. The method of claim 88 in which the mammal suffers from hypercholesterolemia.

96. The method of claim 88 wherein the mammal suffers from a tumor whose growth is stimulated by endogenous growth hormone.

97. The method of claim 88 in which the mammal suffers from a tumor which secretes growth hormone.

98. The method of claim 96 in which the mammal suffers from a tumor whose growth is stimulated by autocrine secretions of growth hormone.

99. The DNA molecule of claim 10 where in said polypeptide the amino acid corresponding to Gly-119 of bovine growth hormone is not proline.

100. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with arginine.

101. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with lysine.

102. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with tryptophan.

103. The DNA molecule of claim 81 where said

substitution corresponding to Gly 119 is with leucine.

104. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with proline.

105. The DNA molecule of claim 81 where the amino acid sequence of said mutant further comprises at least one other substitution of an amino acid of said vertebrate growth hormone said other substitution being at a position outside the third alpha helix thereof.

106. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 50% identical to the third alpha helix of a vertebrate growth hormone.

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